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TITLE: Tau and Beta-Amyloid Deposition, Micro hemorrhage and Brain Function after Traumatic Brain Injury in War Veterans

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14. ABSTRACT

Background:

Studies suggest an increased risk of Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) after traumatic brain injury (TBI). Greater understanding of the chronic effects of TBI may lead to new therapies. This proposal will add a TBI cohort, tau PET imaging and 7T-MRI to the Australian Imaging Biomarkers and Lifestyle - Veterans study (AIBL-VETS) of post-traumatic stress disorder and neurodegeneration. AIBL researchers have an outstanding international record in the development of tau and amyloid PET imaging.

Hypothesis:

1. Veterans with war related TBI have increased tau and AD biomarkers, compared to veterans without TBI.
2. The acute clinical severity of TBI will relate to the extent of positive biomarkers and areas with evidence of focal brain trauma will show more tau and beta-amyloid.
3. Veterans with TBI will demonstrate focal and widespread changes in white matter integrity.
4. 7T-MRI will reveal more extensive microhemorrhage than seen on 3T-MRI and this will relate to traumatic axon injury and cognitive impairment.

Rationale:

The development of brain imaging techniques for in-vivo examination of tau, amyloid and structural integrity now allows study of the chronic effects of TBI and its relationship to AD and CTE.

Specific Aims:

1. To determine if veterans with TBI are more likely to have AD or CTE markers such as beta-amyloid or tau.
2. To determine the relationship between the severity, location and timing of TBI to the extent of positive markers for tau and beta-amyloid.
3. To establish a cohort for long-term study to confirm prognostic significance.

Study Design:

A prospective study of the pathological and neurodegenerative effects of TBI in veterans.

Relevance:

Better understanding of the chronic consequences of TBI will lead to the development of treatment and prevention strategies for cognitive decline and dementia in veterans and in the general population.

15. SUBJECT TERMS Nothing listed					
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1. Introduction

The project will utilize tau, amyloid and FDG PET imaging, and MRI as well as clinical and neuropsychological tools to identify war veterans at risk of Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) as a result of traumatic brain injury (TBI) sustained during military service. Greater understanding of the chronic effects of TBI will lead to better care of veterans and potentially to new therapies to prevent dementia.

The specific aims of this work are:

1. To determine if veterans with TBI are more likely to have markers of AD or tau based disorders such as CTE.
2. To determine the relationship between the severity and timing of TBI to the extent of positive markers for tau and beta-amyloid and the extent of chronic damage including white matter disruption, microhaemorrhage, brain hypometabolism and atrophy, and cognitive impairment.
3. To establish a cohort for long-term study to confirm the prognostic significance of our findings.

2. Keywords

Traumatic Brain Injury, Alzheimer's, Tau, Beta Amyloid, PET, 7T-MRI

3. Accomplishments

What were the major goals and objectives of the project?

Second Year Goals

Milestone 4: Recruitment, clinical & cognitive evaluation of 70% of TBI cohort (n=35). MRI, amyloid, FDG PET scanning of 50% of TBI cohort (n=25). Tau PET complete for 45% of TBI, PTSD & control cohort (n=68).

Estimated completion: September 2015

Milestone 5: Recruitment, clinical & cognitive evaluation of 100% of TBI cohort (n=50). MRI, amyloid, FDG PET scanning of 75% of TBI cohort (n=38). Tau PET complete for 60% of TBI, PTSD & control cohort (n=90).

Estimated completion: December 2015

Milestone 6: MRI, amyloid, FDG PET scanning of 100% of TBI cohort (n=50). Tau PET complete for 80% of TBI, PTSD & control cohort (n=120).

Estimated completion: March 2016

Milestone 7: Tau PET complete for 100% of TBI, PTSD & control cohort (n=150).
Estimated completion: June 2016

Milestone 8: Data analysed and submitted for presentations and publication in collaboration with ADNI-DOD investigators. De-identified data uploaded to the LONI – AIBL - ADNI data centre and released.
Estimated completion: 25th September 2016

What was accomplished under these goals?

- Data was presented at:
    - The Human Amyloid Imaging conference on 13-January-16 in Miami, USA.
    - The NHMRC National Institute for Dementia Research conference on 1-May-2016 in Brisbane, Australia.
    - The Society of Nuclear Medicine conference on 15-June-2016, San Diego, USA.
    - The Alzheimer's Association International conference on 25-July-2016, in Toronto, Canada.
    - Austin Health research week on 4-October-16 in Melbourne, Australia.
    - The Australasian Neuroscience Society conference on 6-December-16 in Hobart, Australia.
- Of proposed 50, **26 veterans with a history of head injury** were recruited, passed screening and are now undergoing PET & MRI scans.
- Of proposed 50, **49 veterans with PTSD** were recruited, passed screening and are now undergoing PET & MRI scans.
- Of proposed 50, **28 veteran controls** were recruited, passed screening and are undergoing PET & MRI scans.
- 97 of the proposed 150 participants have attended a tau PET scan: 28 controls; 45 PTSD; 24 TBI.
- **An extension without funds** has been sought and approved by the USAMRMC

What opportunities for training and professional development did the project provide?

PhD candidate and study coordinator, Tia Cummins, presented data at the NHMRC National Institute for Dementia Research conference in Brisbane, Australia, and the Alzheimer's Association International conference in Toronto, Canada. Immediately following AAIC, Ms Cummins travelled to Boston where she spent a week meeting other lab groups working in the area of dementia, neuroimaging and TBI.
In December, Ms Cummins will present data at the Australasian Neuroscience Society conference, in Hobart, Australia.

How were the results disseminated to communities of interest?

- Data was presented at:

- The Human Amyloid Imaging conference on 13-January-16 in Miami, USA.
- The NHMRC National Institute for Dementia Research conference on 1-May-2016 in Brisbane, Australia.
- The Society of Nuclear Medicine conference on 15-June-2016, San Diego, USA.
- The Alzheimer's Association International conference on 25-July-2016, in Toronto, Canada.
- Austin Health research week on 4-October-16 in Melbourne, Australia.
- The Australasian Neuroscience Society conference on 6-December-16 in Hobart, Australia.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

- The Dept. of Veterans Affairs in Australia has agreed to post out study letters of invitation to veterans registered as having sustained TBI during their service.
- The study team will continue to liaise with the local veteran organizations in a bid to boost recruitment.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Due to the development of methods throughout the current study, the investigators have been invited to join consortia investigating traumatic brain injury, and its impact on risk for dementia.

What was the impact on society beyond science and technology?

Nothing to report.

5. Changes / problems

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

It has been difficult recruiting veterans with a history of TBI. To overcome this, a call for volunteers has been placed in veteran publications, specifically targeting veterans with head injury. These articles have also included brief descriptions on what constitutes a TBI. The Dept. of Veterans Affairs in Australia has agreed to post out study letters of invitation to veterans registered as having sustained TBI during their service. Due to

these delays in recruitment, an extension without funds has been sought and approved by the USAMRMC.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. Products

Conference presentations

Conference: Human Amyloid Imaging conference
Date: 13-15 Jan 2016
Location: Miami, Florida
Title: In vivo assessment of markers of Aβ & tau pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder
Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The NHMRC National Institute for Dementia Research conference
Date: 1-2 May 2016
Location: Brisbane, Australia
Title: Assessing Aβ & tau pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder
Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Society of Nuclear Medicine conference
Date: 11-15 June 2016
Location: San Diego, USA
Title: Assessing AD pathology in Vietnam war veterans with Traumatic Brain Injury & chronic Post-Traumatic Stress Disorder
Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Alzheimer's Association International conference

Date: 23-28 July 2016

Location: Toronto, Canada

Title: In vivo assessment of markers of Alzheimer's disease pathology in Vietnam war veterans with Traumatic Brain Injury & Post-Traumatic Stress Disorder

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Australasian Neuroscience Society conference

Date: 4-7 Dec 2016

Location: Hobart, Australia

Title: Neuropathological markers of Alzheimer's disease in Vietnam war veterans with Traumatic Brain Injury & Post-Traumatic Stress Disorder

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

7. Participants & other collaborating organizations

What individuals have worked on the project?

Name: Christopher Rowe

Project Role: PI

Researcher identify: ORCID no. 0000-0003-3910-2453

Nearest person month worked: 1.2

Contributions to project: As PI, Prof. Rowe has been responsible for the overall management and study integrity, including management and monitoring of collaborative relationships, finances, personnel, ethical compliance & all other aspects of the study.

Funding support: Hospital salary & NHMRC fellowship

Name: Victor Villemagne

Project Role: Co-PI

Researcher identify: N/A

Nearest person month worked: 0.6

Contributions to project: A/Prof Villemagne has had substantial intellectual input, assisted with data analysis, publication and presentation of results.

Funding support: NHMRC fellowship

Name: Malcolm Hopwood

Project Role: Co-PI

Researcher identify: ORCID no. 0000-0001-6004-4521

Nearest person month worked: 0.6

Contributions to project: Prof. Hopwood has had intellectual input into data analysis, publication and presentation of results.

Funding support: University of Melbourne

Name: Tia Cummins

Project Role: Graduate Student & study coordinator

Researcher identify: ORCID no. 0000-0003-3592-0838

Nearest person month worked: 12

Contributions to project: Ms. Cummins handles day-to-day management of the study. She oversees recruitment, bookings, grant applications, ethics submissions, liaising between study team and collaborators, data entry, and maintenance of study records. In February 2015, Ms Cummins began her PhD on the study, Tau and beta-amyloid deposition, micro hemorrhage and brain function after traumatic brain injury in war veterans.

Funding support: NHMRC grant

Name: Robert Williams

Project Role: PET Technician

Researcher identify: ORCID no. 0000-0001-6060-5042

Nearest person month worked: 2

Contributions to project: Mr Williams is PET technician at the Florey institute of neuroscience and mental health. His main role is acquisition of PET images, and assisting with image analysis.

Funding support: University of Melbourne

Name: Alby Elias

Project Role: Graduate student

Researcher identify: ORCID no. 0000-0002-7494-1028

Nearest person month worked: 6

Contributions to project: Dr. Elias carries out psychiatric assessment of participants, and is a PhD student working with the data obtained from the PTSD cohort. The title of his thesis is Post-Traumatic Stress Disorder and Risk of Alzheimer's Disease

Funding support: Piramal pharmaceuticals grant

Name: Fiona Lamb
Project Role: Neuropsychologist
Researcher identify: N/A
Nearest person month worked: 4.8
Contributions to project: Dr Lamb's main role on the study involves cognitive assessment, and clinical review of each participant. In addition, Dr Lamb assists with data interpretation and intellectual input.
Funding support: USAMRMC grant

Name: Rodney Guzman
Project Role: research nurse
Researcher identify: N/A
Nearest person month worked: 3
Contributions to project: Mr Guzman assists the PET technician on scanning days, administering radiotracer doses, and completing data entry. On other occasions, Mr Guzman assists with administrative duties.
Funding support: USAMRMC grant

Name: Paschal Alexander
Project Role: medical officer
Researcher identify: N/A
Nearest person month worked: 1.8
Contributions to project: Dr Alexander provides medical cover during the scanning days, and carries out medical duties on other occasions.
Funding support: USAMRMC grant

Has there been a change in the other active support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations have been involved as partners?

Nothing to report

8. Appendices

HAI Conference abstract:

In vivo assessment of markers of Aβ & tau pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder

Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V, Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Background: Epidemiological studies indicate a nearly twofold increase in risk of dementia associated with Post Traumatic Stress Disorder (PTSD) in military cohorts; however mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with chronic combat related PTSD show evidence of Alzheimer's disease (AD) pathological markers, as assessed by amyloid and tau imaging with PET.

Methods: Sixty-seven male participants -30 veterans with chronic PTSD (aged 67.9±2.6 years) and 37 controls (aged 74.3±8.3 years)- underwent both tau and amyloid PET imaging scans with ^{18}F-AV1451 and ^{18}F-florbetaben or ^{18}F-flutemetamol, respectively. While ^{18}F-AV1451 SUVR was calculated using the cerebellar cortex as reference region, the whole cerebellum and the pons were used as reference regions for ^{18}F-florbetaben and ^{18}F-flutemetamol, respectively.

Results: Despite the PTSD cohort being significantly younger than the controls, there was a significant difference in ^{18}F-AV1451 retention between the PTSD and control groups in the temporoparietal (1.21±0.12 vs. 1.13±0.13, p=0.017) and frontotemporal (1.14±0.12 vs. 1.06±0.13, p=0.018) regions. A similar, albeit not significant, trend was observed in the mesial temporal cortex (1.19±0.12 vs. 1.12±0.17, p=0.058). There was no significant difference in A□ burden between the groups.

Conclusions: Our preliminary findings suggest that chronic PTSD might be associated with higher neocortical tau deposition later in life. More studies to confirm these results are warranted.

SNM conference abstract:

Assessing AD pathology in Vietnam war veterans with Traumatic Brain Injury & chronic Post-Traumatic Stress Disorder

Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V, Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Background: Epidemiological studies indicate a nearly twofold increase in risk of dementia associated with Post Traumatic Stress Disorder (PTSD) in military cohorts, however mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with chronic combat related PTSD show evidence of Alzheimer's disease (AD) pathological markers, as assessed by amyloid and tau imaging with PET.

Methods: Sixty-seven male participants -30 veterans with chronic PTSD (aged 67.9±2.6 years) and 37 controls (aged 74.3±8.3 years)- underwent both tau and amyloid PET imaging scans with ^{18}F-AV1451 and ^{18}F-florbetaben or ^{18}F-flutemetamol, respectively. While ^{18}F-AV1451 SUVR was calculated using the cerebellar cortex as reference region, the whole cerebellum and the pons were used as reference regions for ^{18}F-florbetaben and ^{18}F-flutemetamol, respectively.

Results: Despite the PTSD cohort being significantly younger than the controls, there was a significant difference in the age-corrected ^{18}F-AV1451 retention between the PTSD and control groups in the mesial temporal cortex (1.19±0.12 vs. 1.12±0.17, p=0.03), temporoparietal (1.21±0.12 vs. 1.13±0.13, p=0.01) and frontotemporal (1.14±0.12 vs. 1.06±0.13, p=0.012) regions. There was no significant difference in amyloid burden between the groups

Conclusions: Our preliminary findings suggest that chronic PTSD might be associated with higher neocortical tau deposition later in life. Further work is required to determine if chronic PTSD itself, or associated lifestyle factors account for this observation.

NHMRC NNIDR conference abstract:

Assessing Aβ & tau pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder

Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V, Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Background: Epidemiological studies indicate a nearly twofold increase in risk of dementia associated with Post Traumatic Stress Disorder (PTSD) in military cohorts, however mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with chronic combat related PTSD show evidence of Alzheimer's disease (AD) pathological markers, as assessed by amyloid and tau imaging with PET.

Methods: Sixty-seven male participants -30 veterans with chronic PTSD (aged 67.9±2.6 years) and 37 controls (aged 74.3±8.3 years)- underwent both tau and amyloid PET imaging scans with 18F-AV1451 and 18F-florbetaben or 18F-flutemetamol, respectively. While 18F-AV1451 SUVR was calculated using the cerebellar cortex as reference region, the whole cerebellum and the pons were used as reference regions for 18F-florbetaben and 18F-flutemetamol, respectively.

Results: Despite the PTSD cohort being significantly younger than the controls, there was a significant difference in the age-corrected 18F-AV1451 retention between the PTSD and control groups in the mesial temporal cortex (1.19±0.12 vs. 1.12±0.17, p=0.03), temporoparietal (1.21±0.12 vs. 1.13±0.13, p=0.01) and frontotemporal (1.14±0.12 vs. 1.06±0.13, p=0.012) regions. There was no significant difference in amyloid burden between the groups.

Conclusions: Our preliminary findings suggest that chronic PTSD might be associated with higher neocortical tau deposition later in life. Further work is required to determine if chronic PTSD itself, or associated lifestyle factors account for this observation.

AAIC conference abstract:

In vivo assessment of markers of Alzheimer's disease pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder

Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L. and Rowe, C.C.

Background: Epidemiological studies indicate a nearly twofold increase in risk of dementia associated with Post Traumatic Stress Disorder (PTSD) in military cohorts; however mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with chronic combat related PTSD show evidence of Alzheimer's disease pathological markers, as assessed by amyloid, tau and glucose metabolism using PET.

Methods: Sixty-seven male participants -30 veterans with chronic PTSD (aged 67.9±2.6 years) and 37 controls (aged 74.3±8.3 years)- underwent both tau and amyloid PET imaging scans with ^{18}F-AV1451 and ^{18}F-florbetaben or ^{18}F-flutemetamol, respectively. Fifty-two of these participants (24 PTSD, 28 NC) also underwent ^{18}F-FDG. While ^{18}F-AV1451 SUVR was calculated using the cerebellar cortex as reference region, the whole cerebellum and the pons were used as reference regions for ^{18}F-florbetaben and ^{18}F-flutemetamol, respectively. The posterior cortex (lateral temporal, parietal, posterior cingulate) normalized to cerebellar cortex was used for ^{18}F-FDG.

Results: Despite the PTSD cohort being significantly younger than the controls, there was significantly higher ^{18}F-AV1451 retention in the PTSD group in the mesial temporal cortex (1.19±0.12 vs. 1.12±0.17, p=0.03), temporoparietal (1.21±0.12 vs. 1.13±0.13, p=0.017) and frontotemporal (1.14±0.12 vs. 1.06±0.13, p=0.018) regions. Additionally, ^{18}F-FDG retention in the posterior cortex (lateral temporal, parietal, post cingulate) was significantly lower in the PTSD group when compared to the control group (1.04±0.06 vs. 1.09±0.09, p=0.019). There was no significant difference in A□ burden between the groups.

Conclusions: Our preliminary findings suggest that chronic PTSD might be associated with higher neocortical tau deposition and deficits in glucose metabolism later in life. More studies to confirm these results are warranted.

ANS conference abstract:

Neuropathological markers of Alzheimer's disease in Vietnam war veterans with Traumatic Brain Injury & Post-Traumatic Stress Disorder

Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L. and Rowe, C.C.

Background: Epidemiological research indicates that amongst veterans, both Traumatic Brain Injury and Post-Traumatic Stress Disorder are associated with a 2-4-fold increase in risk of dementia; however, mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with TBI and PTSD show evidence of Alzheimer's disease pathological markers, as assessed by amyloid, tau and glucose metabolism using PET.

Method: 82 male participants -41 veterans with chronic PTSD (aged 68.12 ±2.43 years), 18 with a TBI (aged 68.19 ±2.44 years) and 22 controls (aged 69.63 ±5.29 years)- underwent FDG, tau (18F-AV1451) and amyloid PET (18F-Florbetaben). The Standardized Uptake Value Ratio (SUVR) was calculated using the cerebellar cortex as reference region for all tracers.

Results: The TBI cohort demonstrated significantly higher 18F-AV1451 retention than the control group in the temporo-parietal region (1.23 ± 0.10 vs 1.17 ± 0.08, p=0.044) and frontal cortex (1.18 ± 0.10 vs 1.11 ± 0.09, p=0.044). In addition, 18F-FDG retention in the frontal cortex was significantly lower in the PTSD group when compared to the controls (1.03 ±0.06 vs. 1.07 ±0.07 p=0.014). There was no significant difference in A□ burden between the groups.

Conclusions: These preliminary findings suggest that TBI is associated with later life tau deposition, whilst chronic PTSD is associated with hypometabolism later in life. More studies to confirm these results are warranted.